Challenges in the clinical assessment of novel tuberculosis drugs

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ABSTRACT

To effectively tackle the global TB epidemic, novel treatment strategies are critically needed to shorten the duration of TB therapy and treat drug-resistant TB. Drug development for TB, stymied for decades, has enjoyed a renaissance over the past several years. However, development of new TB regimens is hindered by the limitations in our understanding and use of preclinical models; the paucity of accurate, early surrogate markers of cure, and challenges in untangling the individual contributions of drugs to multidrug regimens in a complex, multi-compartment disease. Lack of profit motive, advocacy, and imagination has contributed mightily to the dearth of drugs we have on the shelf to treat this ancient disease. Areas that will speed the development of new regimens for TB include novel murine and in vitro pharmacodynamics models, clinical endpoints that are not culture-based, innovative clinical trial designs, and an infusion of much-needed funding.

Key words or short phrases (limit 6 to 10): tuberculosis, mouse model, hollow fiber model, pharmacokinetic/pharmacodynamic, translational science, trial design

1. INTRODUCTION[1]

Tuberculosis (TB) is surpassed only by HIV as a cause of infectious disease-associated death worldwide. Novel treatment strategies are critically needed to shorten the duration of TB therapy and treat drug-resistant TB, an emerging global health threat. Drug development for TB, stymied for decades, has enjoyed a renaissance over the past several years. However, development of new TB regimens is hindered by the limitations in our understanding and use of preclinical models; the paucity of accurate, early surrogate markers of cure; historic use of trial outcome variables that are relatively uninformative with poor statistical properties (e.g. mid-treatment sputum culture conversion); and challenges in untangling the individual contributions of drugs to multidrug regimens in a complex, multi-compartment disease. Lack of imagination (by investigators and industry), profit motive, and advocacy has also contributed mightily to the dearth of drugs we have on the shelf to treat this millennia-old disease.

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2. TUBERCULOSIS: STILL NOT CONTROLLED?

2.1 Drug-sensitive TB: prolonged multidrug treatment for a widely-lethal foe

Among bacteria, *Mycobacterium tuberculosis* is the single greatest killer on the planet. The World Health Organization (WHO) estimates that there were over 9 million new cases and 1.5 million deaths due to TB in 2013 [1]. TB control efforts are hampered by the lengthy, complex treatment regimens necessary for cure without relapse. Although the current regimens and drugs have been very successful in controlled clinical trials with cure rates up to 95%, in practice treatment completion and outcomes vary widely by setting. Currently, under ideal conditions, TB is treated for six months, though in practice, treatment completion often takes longer. So-called "short course" TB therapy includes isoniazid, rifampicin, pyrazinamide, and ethambutol given during the intensive phase (first two months) of therapy followed by isoniazid and rifampicin given during the continuation phase (last four months). The full application of the directly observed therapy short course (DOTS) strategy is becoming more and more difficult in resource-limited settings where TB incidence is high, as these countries are also battling to control the HIV epidemic. There is a need for highly potent TB treatments that can cure disease in substantially fewer than the six months currently required. Shorter treatment duration can decrease the logistical burden and expense of prolonged treatment (given in large part under direct observation), improve adherence, and help prevent the emergence of acquired drug resistance. An urgent research priority is, thus, to evaluate new drugs and new combination regimens that can shorten treatment duration for drug-sensitive TB, both for the benefit of individual patients and to improve TB control from a public health standpoint.

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[1] TB: Tuberculosis
WHO: World Health Organization
DOTS: Directly Observed Therapy Short Course
MDR: Multidrug Resistant
XDR: Extensively Drug Resistant
TDR: Totally Drug Resistant
EBA: Early Bactericidal Activity

2.2 Drug-resistant TB: ushering in the post-antibiotic era- can't we do better?

Multidrug resistant (MDR) TB, TB resistant to isoniazid and rifampicin, is a growing public health threat, with an estimated 480,000 cases in 2013. Extensively drug-resistant (XDR) TB, TB resistant to isoniazid, rifampicin, fluoroquinolones, and injectable anti-TB drugs, has been found in every country in which it has been sought [2]. Additional resistance to drugs beyond those included in the definition of XDR has also been reported, coined by some as "totally drug-resistant (TDR) TB", threatening a return to the pre-antibiotic era of TB management [3-6]. In general, therapeutic options for drug-resistant TB are limited in availability, acceptability, and efficacy. Currently, only 1 in 5 patients diagnosed with MDR-TB is started on treatment [2]. Current treatment for MDR-TB requires ≥20 months of multidrug therapy, including ≥8 months of an injectable agent [7], and yet is successful in only 48% of patients [2], not very different from the cure rates in the pre-antibiotic era-- 30% for sputum smear positive and 80% for sputum smear negative, culture positive TB [8]. In some settings, though, higher success rates have been achieved with intensification of resources and/or enhancement of the treatment regimen [9-11]. Furthermore, MDR-TB treatment regimens are poorly tolerated and have significant toxicities. A common standard regimen, for example, may include kanamycin or amikacin (ototoxicity, which can be irreversible), a fluoroquinolone, ethionamide or prothionamide (dose-limiting gastrointestinal toxicity), pyrazinamide (hepatotoxicity and risk of resistance, as this drug is a standard part of first-line regimens), cycloserine/terizidone (central nervous system toxicity), and ethambutol (ophthalmologic toxicity risk and risk of resistance, as this drug is a standard part of first-line regimens). Having effective new anti-TB drugs and regimens is, thus, not only important to improve cure rates and reduce risk of acquired resistance but also to reduce suffering related to common and severe side effects of standard MDR-TB regimens.

3. PRECLINICAL MODELS OF TB DISEASE- THE TRANSLATIONAL GAP

3.1 Traditional mouse model of TB disease and its treatment

The mouse model of TB disease has been used for more than 50 years for the development and evaluation of new TB drugs and regimens [12]. Although it has been criticized for not recapitulating the clinicopathological manifestations of TB in humans [13], the mouse model of experimental chemotherapy has been instrumental in testing drug combinations and in predicting agents and combinations with treatment-shortening potential. Mice are infected via aerosol or intravenous route, and after 2-3 weeks of infection, bacillary burden approaches that seen in human TB pulmonary cavities. Treatment efficacy is assessed by measuring colony forming units in lung and spleen homogenates at various intervals during treatment, and relapse is assessed 3-6 months after discontinuation of a test regimen. The mouse model successfully discriminates between drugs with good bactericidal but limited sterilizing activity (isoniazid and streptomycin) and those with treatment-shortening potential (rifampicin and pyrazinamide) [14]. The model is simple, inexpensive, tractable, and has the highest predictive value for clinical efficacy of combination regimens of any preclinical model [15]. Every drug regimen tested clinically for TB treatment in the 21st century has been tested first in the mouse model. It is important, though, to understand the strengths and limitations of this model, lest we overestimate its translational value.

3.2 Recognizing the strengths and limitations of the mouse model—optimizing its translational value

The mouse model is an important tool for TB drug development. In particular, it is useful for creating early knowledge about exposure-response (or pharmacokinetic/pharmacodynamic) relationships, for determining the pharmacodynamic driver of individual drug activity (e.g. does the drug display time-dependent or concentration-dependent killing), and for identifying combination regimens with promising bactericidal and sterilizing activity that merit clinical testing. However, the model has limitations that have to be taken into account when interpreting efficacy data deriving from mouse experiments. First, tubercle bacilli in mouse lungs reside intracellularly, whereas the majority of bacilli in human disease are located extracellularly in necrotic granulomas and cavitary lesions. The pathology in mice and humans is simply different, and this may affect drug distribution and activity, which may, in turn, influence the drug exposures and treatment duration required for cure. Furthermore, mouse models do not and cannot reproduce the tremendous variability we see in human disease. Disease burden, anatomic location of infection, *M. tuberculosis* strain, drug pharmacokinetics, and immune system contribution to cure differ widely from person to person. In contrast, in mouse models, experimental conditions are deliberately standardized so that the activity of specific drugs and regimens can be cleanly characterized. Up to now, the clinical trials community has overestimated the mouse model's ability to directly inform selection of dose and treatment duration for treatment trials in human TB, and this has hindered TB drug development [16-20]. Enhancing quantitative assessment of mouse model results, including use of systems pharmacology approaches or multiscale modeling to help us understand the contributions of infecting strain, immune system, pharmacokinetic variability, and pathology to bacterial killing and sterilizing activity of regimens, with links to results from human clinical trials in which relapse is assessed is the way forward for optimizing use of the mouse model for clinical prediction. In addition, other new preclinical tools such as *in vitro* pharmacodynamics systems (hollow fiber models), animal models that develop human-like disease (like C3HeB/FeJ mice, the "Kramnik" mouse model), and imaging modalities that allow us to assess drug distribution at the site of disease may be instrumental in filling knowledge gaps that preclude full mouse-to-human translation [15, 21]. Investment in this "translational space" to broaden our understanding of what preclinical models are telling us (or not telling us) will help drive more efficient and effective clinical development of novel TB regimens. This is especially important given the large number of existing and investigational drugs for TB and, thus, the near-limitless number of potential drug combinations to test.

4. SURROGATE MARKERS FOR CLINICAL CURE- WHAT CAN WE MEASURE?

4.1 Tuberculosis: a complex disease with a complex treatment

TB in humans is a complex disease that primarily affects the lung in discrete consolidated foci known as granulomas. In contrast to murine models of TB disease, human disease is characterized by discrete types of lesions including aerobic cavities and anaerobic caseous necrotic nodules. The bacteria found in these different anatomical compartments are thought to represent metabolically distinct populations that have adapted to their local milieu [22]; further, the activity of individual TB drugs varies depending on the metabolic state of the bacteria [23]. Isoniazid, for example, has potent bactericidal activity against TB under aerobic conditions, like in cavities, while rifampicin is the most effective agent against bacteria located in anaerobic, necrotic lesions. To cure TB, a treatment regimen is most likely to be effective if it contains drugs that do the following: kill rapidly-dividing bacilli, thus bringing down the bacterial burden rapidly (isoniazid); eliminate semi-dormant bacteria, so-called "persisters," that lead to relapse (rifampicin and pyrazinamide); and protect companion drugs against

emergence of resistance (a mechanism that is attributed to ethambutol). Assessment of an individual drug's contribution to bactericidal activity, sterilizing activity, and prevention of acquired resistance in the context of multidrug treatment is challenging, yet any effective drug combination must have all these features, in addition to being safe and tolerable. In addition, drugs differ in their ability to penetrate the various lesions found in human pulmonary TB disease. Imaging modalities such as positron emission tomography (PET) of radiolabelled drug and matrix assisted laser desorption/ionization (MALDI) are emerging as technologies that may be helpful in assessing drug distribution and assuring adequate drug concentrations at the site of disease [21, 24].

4.2 Microbiologic markers of treatment response

For assessment of TB treatment response, we are limited to biological samples we can reasonably collect. For hepatitis C, understanding of the complex relationship between viral kinetics and sustained virologic response among treated patients revolutionized our ability to predict, early in treatment, which patients will be cured by therapy [25]. Similarly, mathematical modeling of HIV-1 viral kinetics in different biological compartments with antiretroviral treatment contributed significantly to our understanding of treatment-response relationships for this infection [26]. While HIV or hepatitis C viral load in plasma is informative and easy to obtain, we cannot so readily access the compartments where TB lives and TB drugs must act. Since 1973, TB treatment trials have reported results of sputum culture collected two months after treatment initiation as a marker of treatment efficacy [27], yet we know that viable bacteria remain in lungs of patients with negative two-month cultures and that therapy beyond two months is required for durable cure. Compounding this is the fact that cough and the ability to expectorate diminishes during treatment, despite the presence of live bacilli in the lungs, such that sputum-based measures for treatment effect are no longer informative. The limit of detection of sputum microscopy (point-of-care test) for presence of *M. tuberculosis*, $\leq 10^4$ bacteria per mL of sputum, is reached early in treatment, and sputum cultures (for which results are available in 1-2 months) are negative for 95% of patients within 3 months of treatment initiation [28]. Further, sputum culture has poor sensitivity for identifying patients who will subsequently relapse-- 48% in one re-analysis of 12 clinical trials [29]. In the absence of efficient markers to predict individual outcomes, there was hope that these surrogate microbiologic markers could at least distinguish differences between regimens in trials. Unfortunately, in contemporary trials aimed at testing shorter-duration regimens, the treatment effect on two-month culture positivity was noted to be favourable in the experimental arms, but the effect on the relevant clinical outcome (cure without relapse) was insufficient [30-32]. A recent meta-analysis further highlighted the poor predictive capability of sputum smears and cultures during treatment for predicting relapse [33]. Lastly, existing regimens achieve high (90-99%) culture conversion rates after two months of therapy, limiting the usefulness of this biomarker to discriminate among treatment-shortening regimens [17]. Although other microbiologic biomarkers have been proposed as surrogate endpoints in TB treatment trials, including quantitative cultures on solid medium or time-to-detection on liquid medium, none have been validated as surrogate endpoints in Phase 3 trials [34-36]. The lack of a biological marker that can be collected early in treatment that can serve as a reliable and accurate surrogate endpoint for cure in TB treatment trials has been a significant impediment to advancing new drugs to the market.

4.3 Moving beyond sputum culture—other surrogate markers

M. tuberculosis is a slow-growing organism, so for any culture-based marker of treatment response, there is a delay of months between specimen collection and availability of results. Molecular markers of treatment efficacy are appealing because they can be measured with great sensitivity and, for some assays, in real time, allowing for more efficient comparisons of treatments. Whereas nucleic acid amplification tests (NAAT) that detect mycobacterial DNA in sputum (such as GeneXpert MTB/RIF (Xpert)) can quantify the initial amount of mycobacteria very well [37], they overestimate the amount of still-viable mycobacteria in sputum due to detection of residual DNA of dead mycobacteria [38]. To overcome this obstacle, novel technologies selectively amplifying 16S ribosomal RNA as well as "genome wide" mRNA targets are being evaluated. Evaluations of 16S ribosomal RNA have shown that the results obtained in as little as 4 hours correlate well with culture results during therapy [39]. Evaluation of host- and/or pathogen-derived products that predict treatment response and correlate with relapse, though, is a science in its infancy, and issues with multiple comparisons, challenges in distinguishing relapse from recurrence, and reverse temporality impact its validation [40, 41]. However, recently transcriptomics, metabolomics, and other high-throughput methods have been employed to strengthen our understanding both of *M. tuberculosis* physiology and persistence and of host-organism signature patterns in patients who are successfully treated versus those who are not [42] Validating these markers is slow and arduous given the rarity of treatment failure or relapse with standard treatment and the small number of Phase 3 trials assessing these outcomes with new or shortened regimens. Investment in this high-risk though potentially high-yield area, though, is essential. To support late-stage research targeting validation of TB Biomarkers of treatment effect, the Consortium for TB Biomarkers has been formed with funding from the National Institutes of Health, Food and Drug Administration, and Bill and Melinda Gates Foundation. A biorepository of samples from a target of 1000 patients enrolled in longitudinal cohorts, including Phase 3 trials, is now available for access through a peer review system (www.tbbiorepository.org). Until a better early biomarker of sterilizing activity in humans is identified, the selection of drug regimens with the highest treatment-shortening potential for Phase 3 trials cannot be made with confidence. Unfortunately, this also means that the TB drug development field will continue to experience costly Phase 3 trial failures.

5. OPTIMIZATION OF TRIAL DESIGN

5.1 Clinical development of a TB drug—the "established" pathway

All new TB regimens must ultimately be tested in human populations in large-scale, well-powered studies. Historically, after initial Phase I safety and pharmacokinetic (PK) studies, middle- and late-phase clinical evaluation of TB drugs have proceeded sequentially from Phase 2A studies of early bactericidal activity (EBA) to Phase 2B and Phase 3 trials (Figure 1). In EBA studies, first introduced in 1980 by Jindani *et al* [43], patients with sputum culture-positive pulmonary TB are given monotherapy for a short, ethically-acceptable period of time (typically 7-14 days), daily sputum samples are collected, and the log decline in sputum colony counts per unit time is compared to that of TB drugs with known efficacy. If efficacy is shown in an EBA trial, either from Days 0-2 (a measure of early bactericidal activity) or from Days 2-14 (a putative measure of sterilizing activity), drug development has proceeded. EBA studies thus have served as "proof-of-concept" trials – the goal is to demonstrate measurable microbiologic activity of the test agent when it is given alone. EBA trials are also used for dose finding and to determine an early safety profile using a limited number of patients. Multiple different doses or dosing schemes are typically evaluated, and the "winners" are moved into Phase 2B testing.

Phase 2B trials are traditionally eight weeks in duration, and multidrug therapy is given. Sputum samples are collected for culture on a regular basis over the experimental treatment phase. After the eight-week intensive phase is complete, study participants are transitioned to standard, non-experimental continuation phase treatment, typically administered by the local TB program (for drug-sensitive TB, this is typically isoniazid and rifampicin to complete 6 months of therapy). The proportion of participants who have converted their sputum cultures to negative by eight weeks of treatment is compared across arms; time to culture negativity is also assessed by arm. An improvement in culture conversion at eight weeks of at least 13% with the test regimen compared to standard treatment has been proposed to demonstrate activity potentially sufficient to warrant shortening the duration of treatment of a regimen and moving to Phase 3 trials [34, 44]. This was based on the fact that a 13% improvement in culture conversion was seen with the inclusion of pyrazinamide in the intensive phase of treatment, leading to a reduction of treatment duration from 9 months to 6 months [45]. Others have suggested a hazard ratio of 1.8 or higher, comparing time to culture conversion in the experimental arm to the control arm [46].

In classic Phase 3 trials for drug-sensitive TB, an experimental 4-month treatment must be non-inferior to standard 6-month therapy, using failure or relapse as the endpoint. Using that design, phase 3 trials require about 500-1000 participants per arm, 12-18 months of post-treatment follow-up, and up to 150 million US dollars of investment. The human and economic cost of an error in study design or the wrong choice of drug dose or combination in this setting is exceedingly high. For MDR-TB, improvement in culture conversion at specified time points (2 months or 6 months) when the experimental drug is added to multidrug background therapy compared to multidrug background therapy plus placebo has been sufficient for initial registration of the drug by US and other regulators, with final approvals conditional on achieving favourable results in confirmatory late-stage phase 3 clinical trials.

5.2 Limitations of the classic TB drug development paradigm

EBA studies, while helpful in some circumstances, may be misleading. In later studies by Jindani and colleagues, isoniazid had the most impressive log drop in *M. tuberculosis* colony counts over the first two days of therapy of any other drug, consistent with its known potent bactericidal activity. Rifampicin and streptomycin had the highest Day 2-14 EBA, pointing to a possible role of these agents later in treatment [47]. Pyrazinamide had no activity, and ethambutol antagonized the sterilizing activity of other drugs. These results are not consistent with later-phase clinical trials, which showed that streptomycin only has sterilizing activity during the first month and that pyrazinamide is a powerful treatment-shortening agent with effective sterilizing activity. Further, we cannot assume that the dose that provides the maximal EBA in a 14-day Phase 2A trial will also provide optimal activity over an 8-16 week treatment, but this is hard to test given the constraints on the number of arms and doses that can be tested in a Phase 2B or 3 format. In Phase 2B trials, the experimental treatment is stopped at eight weeks, so the safety and efficacy of longer-duration therapy are not assessed, and links between microbiologic outcomes and relapse are not explored. Phase 2B trials, thus, tell us little about how much treatment shortening can be expected from a promising regimen. In addition, the confidence intervals around estimates of microbiologic endpoints in a Phase 2B trial may be wide, further complicating interpretation of results.

Several Phase 3 failures have occurred in the recent past, of regimens that passed “go/no go” criteria in early phase trials [30-32]. In the Phase 3 trials, two-month culture conversion was marginally better in the experimental arms than the control arms; relapse was unacceptably high in all 4-month treatment arms. A shortened TB regimen must cure all patients, including patients who are harder to

treat because they have more extensive disease, lower drug concentrations, or other characteristics that put them at higher risk of inadequate treatment response. Up to now, standard Phase 2A and 2B studies have shown us how to identify shorter regimens to treat the average patient (over 80% of patients were cured with the recent "failed" Phase 3 regimens) but not how to design a shortened treatment regimen that benefits all patients. Biomarkers that would allow us to identify those patients who can be cured with shortened regimens are badly needed and could potentially help us avoid costly phase 3 failures.

5.3 Innovative design strategies to maximize learning from middle development trials and chance of success of definitive trials

There are multiple new drugs in the pipeline and dozens of potential combinations employing new drugs and optimized doses of existing drugs. Building a wholly new regimen by assessing single drug substitutions (of a new drug for an old one) one at a time will take more than a decade. On the other hand, testing completely new combinations without intermediate single-substitution studies may advance promising combinations more quickly but can be risky, as the contribution of each drug to overall efficacy (in successful and unsuccessful trials) and to drug-related toxicities may be challenging to tease out. By interrogating the clinical development pathway critically, we have increasingly recognized that we spend a lot of effort and resources measuring indicators of efficacy over 14 days (Phase 2A) or over 8 weeks (Phase 2B) that have limited value in predicting long-term clinical outcomes. Until we have more reliable and predictive markers of efficacy, the focus of early clinical development should be on generating safety data for new drugs, alone and in combination. We should aim to generate data on meaningful measures of treatment efficacy (stable culture conversion at the completion of treatment and relapse) as early as possible in drug or regimen development. By combining aspects of both efficacy and safety, can we develop a clinical testing paradigm that maximizes learning from middle development trials and provides the highest chance for success in Phase 3 trials, allowing at the same time for the evaluation of new predictive treatment markers? In Figure 2, we provide some promising strategies, including some that are already being tested in the clinical arena. Phase 2A EBA studies can be extended to allow dosing of the experimental drug beyond 7-14 days, provided that companion drugs are given. In this way, the safety of the investigational product(s) in the context of multidrug therapy can be expressly assessed and drug-drug interactions can be measured to select the optimal dosing of the candidate drug in the novel regimen. Re-randomization after 7-14 days to a single substitution regimen (e.g. first-line drug backbone of isoniazid-rifampicin-pyrazinamide (RHZ) + Drug X vs. Drug Y or novel backbone (Drugs ABC + Drug X vs. Drug Y)) can yield important safety and early efficacy data for drug combinations that inform subsequent longer-duration studies in patients with drug-sensitive and drug resistant TB.. Phase 2B trials should test regimens for the full duration of time that it is anticipated they will be used in a subsequent Phase 3 trial, rather than just 8 weeks, again to capture the fullest information about safety and microbiologic activity of the regimen. Phase 2B trials should be used to assess PK/PD relationships, define PK targets, and determine dosing that will achieve those targets for the majority of patients using mathematical modeling. The broader the range of doses tested, the more likely the optimal dose can be identified and selected for confirmatory trials. Special attention should be paid to those patients who are microbiologic "slow responders" to identify characteristics that may predict poor outcomes; these data should inform the design of later phase trials. A greater number of regimens can be tested in Phase 2B by employing a multi-arm, multi-stage (MAMS) design that features early discontinuation of regimens that fail to show promise at interim analyses.

In the event that there is confidence that a shorter regimen may be curative based on Phase 2A and Phase 2B studies of component agents, a 'Phase 2C' design can be employed directly to bridge the gap to the confirmatory phase 3 trial. In this novel design, the experimental treatment is given for 3 or 4 months, then stopped; continuation phase standard treatment is not given, and patients are followed carefully for relapse. Unlike in Phase 3 studies, the objective is not to demonstrate non-inferiority (requiring large sample sizes) but to rule out unacceptably high relapse rates and, thus, the number of patients can be much smaller and the duration of follow-up can be limited to 6 months post-treatment, a time point that captures more than 90% of patients who will relapse. The primary endpoint is the same intermediate microbiologic or safety endpoint used in current phase 2B trials (and therefore a Phase 2C can replace the established Phase 2B design). In this way, with as few as 80-100 patients per arm, ineffective regimens can be prevented from advancing to expensive phase 3 trials.

Substudies of promising biomarkers should be nested in all Phase 2C and 3 trials, and once quantitative measures of "persisters" are discovered, they should be included in pharmacokinetic/pharmacodynamic analyses so that we understand more completely the effects of different drugs on various bacterial subpopulations.

Lastly, it might be time to reconsider our "one-size-fits-all" approach to TB treatment. With rare exceptions, all patients are treated with the same regimen for the same duration, regardless of their personal characteristics or disease severity. This leads to overtreatment of a large proportion of patients and undertreatment of others—each scenario can be harmful. Carefully designed Phase 3 trials can help us identify those patients who might benefit from shortened treatment, even if others cannot. Similarly, there is no one-size-fits-all approach to TB drug development. The right path for a drug depends on its role in the regimen and the synergies and antagonisms with other drugs, and investigators need to keep that in mind when making decisions about the design of trials and development pathways for new regimens.

6. ADVOCACY, FUNDING, AND INCENTIVES FOR TB DRUG EVALUATION

TB has traditionally been a neglected disease despite its position as the number two cause of mortality by an infectious agent, the number one killer of persons living with HIV infection, and a top five cause of death for women ages 25-44 globally. In its *Global Plan to Stop TB 2011-2015 Report* [48], the World Health Organization declared that significant investment in drug development would be required to reach the goal of a 95% reduction in TB deaths and 90% reduction in TB incidence between 2015 and 2035. From 2011-2015, a total of $3.7 billion was estimated to be required to meet short-term goals for drug development, yet research and development investment fell far short of that, as detailed in the Treatment Action Group's 2015 Pipeline Report [49]. There is little profit motive for companies to develop drugs for diseases that can be cured, and, indeed, several big pharma companies have recently shuttered their anti-infectives units entirely. TB is considered an orphan disease in the United States because of its rarity there, but despite the significant incentives that the Food and Drug Administration provides for registration of products for orphan diseases (including the opportunity to register a drug with Phase 2 data alone, before completion of Phase 3 trials), few drug companies are working on TB, though there are some. Fortunately, some public-private partnerships have moved in to try to fill the gap, bringing together drug companies, academic institutions, and philanthropists in a concerted effort to develop new TB regimens. Governmental agencies such as the US National Institutes of Health and the Centers for Disease Control and Prevention provide substantial support for TB treatment trials along with European Union funding through the European & Developing Countries Clinical Trials Partnership (EDCTP). The Bill & Melinda Gates Foundation is also funding TB work. Advocacy groups, happily,

are increasingly involved. Clinical trials infrastructure is still limited; investment is needed to ensure there are enough high-quality sites to perform much-needed trials work.

7. CONCLUSIONS

In conclusion, there is an urgent need for shorter-duration treatment regimens for drug-sensitive TB and shorter, less-toxic regimens for drug-resistant TB, but drug development for TB is remarkably challenging. Concerted research effort and increased funding will be required to overcome gaps in our understanding so that we can build and use all available tools – across the preclinical-translational-clinical axis -- to bring the best regimens to the people who need them the most in the most efficient way possible.

FIGURES

Figure 1. Established drug development pathway.

Figure 2. Interrogating the established clinical development pathway—toward more efficient and effective evaluation of drug regimens for TB.

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